(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 904 781 A2

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
31.03.1999 Bulletin 1999/13

(51) Int Cl 6 A61K 31/215, A61K 9/14

(21) Application number: 98307588.8

(22) Date of filing: 17.09.1998

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 19.09.1997 CA 2214895

(71) Applicant: SHERMAN, Bernard Charles
Willowdale, Ontario M2L 2K1 (CA)

(72) Inventor: SHERMAN, Bernard Charles
Willowdale, Ontario M2L 2K1 (CA)

(74) Representative: Votier, Sidney David
CARPMAELS & RANSFORD
43, Bloomsbury Square
London WC1A 2RA (GB)

(54) Improved pharmaceutical composition comprising fenofibrate

(57) The bioavailability of fenofibrate is improved by making a solid dispersion of a disentegrant in the fenofibrate. Method of making said solid dispersion comprising melting the fenofibrate, blending the disintegrant into the melt, and resolidifying the mixture.

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Printed by Jouve, 75001 PARIS (FR)

Description

FIELD OF INVENTION

[0001] The present invention relates to pharmaceutical compositions for oral administration comprising fenofibrate which enable improve dissolution and bioavailability.

BACKGROUND

[0002] Fenofibrate is practically insoluble in water. This causes fenofibrate to exhibit a low rate of dissolution in aqueous media (including gastrointestinal fluids), which results in inadequate bioavailability (absorption into systemic circulation) after oral ingestion.

[0003] In order to make a composition comprising fenofibrate that will enable maximum bioavailability, it is necessary to incorporate into the composition a feature that increases the rate of dissolution of the drug to enable it to dissolve in the gastrointestinal fluids.

[0004] Several ways of increasing the rate of dissolution of drugs having low solubility in water are known in the prior art.

[0005] One approach is micronization. In this approach, the drug is milled to fine particles, typically having a mean diameter of only a few microns. A second approach is to include a surfactant in the composition.

[0006] For the drug fenofibrate, neither micronization alone nor use of a surfactant alone enables maximum bioavailability. US Patent 4895726 discloses that the rate of dissolution and the bioavailability of fenofibrate can be maximized by co-micronization of fenofibrate. In this process the fenofibrate is first mixed with the surfactant and then the mixture is micronized.

[0007] A composition made according to the invention of US Patent 4895726 is sold in Canada as elsewhere under the tradename Lipidil Micro. The need for micro-composition and use of a surfactant adds to the cost of capsules containing fenofibrate.

[0008] In view of the limitations of the prior art, it is an object of the present invention to enable maximum bioavailability of fenofibrate without the need for micronization and without the need for use of a surfactant.

DESCRIPTION OF THE INVENTION

[0009] It has been found the rate of dissolution and the bioavailability of fenofibrate can be substantially improved by making a solid dispersion of a disintegrant in the fenofibrate. The solid dispersion can be made by heating and melting the fenofibrate, blending the disintegrant into the molten fenofibrate, and then cooling and solidifying the mixture.

[0010] Fenofibrate has a melting point of about 80°C and can be melted without decomposition.

[0011] A disintegrant will be understood to be a substance which is hydrophilic and swells upon absorption of water. Disintegrants are used as excipients (inactive ingredients) in pharmaceutical tablets and capsules so that, when a tablet or capsule is ingested, the disintegrant will cause the tablet or capsule to absorb gastrointestinal fluid and, as a result, to swell and disintegrate, so as to release the active drug for dissolution and absorption.

[0012] The most commonly used disintegrant is starch.

[0013] Disintegrants with very high capacity to absorb water and swell are known as "super-disintegrants", which include such substances as croscarmellose sodium, sodium starch glycolate and crospovidone.

[0014] As aforesaid, a solid dispersion comprising a disintegrant dispersed in the fenofibrate can be made by melting the fenofibrate, blending the disintegrant into the molten fenofibrate and then cooling and solidifying the mixture. The solid can then be ground into granules for further processing into tablets or capsules.

[0015] Because of the very intimate mixing achieved by mixing the disintegrant into the fenofibrate in the molten state, it follows that each granule or particle of the ground-up solid dispersion will be an approximately uniform mixture of fenofibrate and disintegrant.

[0016] The solid dispersion is thus intrinsically different from a mixture achieved simply by physical mixing of fenofibrate in solid form and disintegrant, because in a physical mix each particle remains either pure fenofibrate or pure disintegrant.

[0017] It will be understood that in the process of making a solid dispersion, within the scope of the present invention, ingredients other than the fenofibrate and disintegrant may be included in the molten blend and thus incorporated into the solid dispersion. Such other ingredients may include, for example, water-soluble or water-insoluble ingredients which serve as surfactant, diluent, or for other purposes.

[0018] Alternatively, other ingredients may be mixed with the granules of solid dispersion, and the mix so achieved may be further processed into tablets or capsules.

[0019] The invention will be further illustrated by the following example, which is intended to be illustrative but not limiting of the scope of the invention.

EXAMPLE 1

[0020] 4800 g of fenofibrate was placed in a stainless steel pot, which was slowly heated until the fenofibrate was melted. 1200 g of croscarmellose sodium was then blended into the molten fenofibrate, and the mix was then poured into trays and allowed to cool and solidify to form a solid dispersion.

[0021] The solid was then removed from the trays and milled through a #10 screen to produce granules.

[0022] 5 kilos of the resulting granules were then mixed with other ingredients as follows:

solid dispersion granules	5.0 kilos
lactose monohydrate	2.84 kilos
stearic acid	0.14 kilos
colloidal silicon dioxide	0.02 kilos
	8.00 kilos

[0023] This mixture was then filled into 2-piece hard gelatin capsules with a net fill weight of 400 mg per capsule. Each capsule thus contained 250 mg of the solid dispersion, which in turn comprised 200 mg of fenofibrate.

[0024] For these capsules, it was found that the dissolution rate and bioavailability was equivalent to that of commercially available Lipidil Micro capsules containing 200 mg of co-micronized fenofibrate and surfactant.

Claims

1. A solid pharmaceutical composition comprising a solid dispersion of a disintegrant in fenofibrate.

2. A composition as in claim 1 wherein the disintegrant is selected from croscarmellose sodium, sodium starch glycolate and crospovidone.

3. A process of making a composition as in either of claims 1 or, 2, which comprises the steps of melting the fenofibrate, blending the disintegrant into the molten fenofibrate, and solidifying the mixture.

4. A process as in claim 3 which further comprises the steps of grinding the resulting solid into granules and further processing the granules into capsules or tablets.

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European Patent Office
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(11) EP 0 904 781 A3

(12) **EUROPEAN PATENT APPLICATION**

(88) Date of publication A3:
03.11.1999 Bulletin 1999/44

(43) Date of publication A2:
31.03.1999 Bulletin 1999/13

(21) Application number: **98307588.8**

(22) Date of filing: **17.09.1998**

(51) Int Cl.[6]: **A61K 31/215**, A61K 9/14

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Printed by Jouve, 75001 PARIS (FR)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 30 7588

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl 6)
A	FR 2 722 984 A (LABORATOIRES EFFIK) 2 February 1996 (1996-02-02) * claims 1-12 * * page 8, line 17 - line 24 *	1-4	A61K31/215 A61K9/14
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TECHNICAL FIELDS SEARCHED (Int Cl 6)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	17 September 1999	Scarponi, U

CATEGORY OF CITED DOCUMENTS

X particularly relevant if taken alone
Y particularly relevant if combined with another document of the same category
A technological background
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T theory or principle underlying the invention
E earlier patent document, but published on, or after the filing date
D document cited in the application
L document cited for other reasons

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EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 98 30 7588

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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17-09-1999

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EPO FORM P0459

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